Focus on....

SGLT2 inhibitors

Lynda Steyn, BPharm

Amayeza Info Services

The on-going search for new therapeutic diabetic agents has led to the focus being redirected to the kidney, and its role in glucose homeostasis.[1] The kidney primarily achieves glucose homeostasis through its ability to reabsorb the glucose that is filtered into the glomerular filtrate.[1] Almost all the glucose that is filtered is reabsorbed and returned into the circulation in healthy individuals, which results in minimal or no glucose being excreted in the urine.[1,2]

Patients with type 2 diabetes (T2DM) have, amongst a number of pathological defects, an increased reabsorption (20–40%) of glucose in the kidneys.[1,3]

Clinical studies of the sodium-glucose co-transporter 2 (SGLT2) inhibitors, canagliflozin, dapagliflozin and empagliflozin, compared to placebo, have shown marked improvements in glycaemic control.[2] Currently in South Africa, only dapagliflozin (Forxiga®) is registered for use in patients with T2DM.[4]

Mode of action

Two sodium-glucose co-transporter proteins, SGLT1 and SGLT2, are involved in the reabsorption of glucose from the glomerular filtrate. SGLT2 proteins are found in the first section of the proximal convoluted tubule (PCT) of the kidney and SGLT1 proteins are found further along the PCT. In healthy persons, approximately 90% of the filtered glucose is reabsorbed by SGLT2, and the remaining 10% by SGLT1.[1,2]

Inhibiting SGLT2 prevents 30–50% of filtered glucose from being reabsorbed, which is then excreted in the urine.[5,6] In patients with hyperglycaemia, the excess glucose is thereby removed from the body and blood glucose is reduced.[2] The resulting glucosuria causes osmotic diuresis, (resulting in a decrease in blood pressure) and weight loss (200–300 kcal/day).[3]

SGLT2 inhibition is dependent on blood glucose levels and independent of insulin activity.[3] When plasma glucose levels drop below 90 mg/dL (5 mmol/l), SGLT2 action becomes negligible.[5] This, together with the fact that their action is independent of insulin, lessens the likelihood of SGLT2 inhibitors causing hypoglycaemia when used alone, or in combination with agents that do not typically cause hypoglycaemia.[5,7]

Indications

SGLT2 inhibitors are indicated for patients with T2DM whose hyperglycaemia is inadequately controlled by diet and exercise.[2]

Dapagliflozin is indicated to improve glycaemic control in type 2 diabetic patients who are 18 years or older.[8]

It is used as:

- *Monotherapy*:* In patients with T2DM, together with diet and exercise
- *Add-on combination therapy:* In patients for whom other glucose-lowering agents, together with diet and exercise, are not providing sufficient glycaemic control. Dapagliflozin may be used in combination with metformin, thiazolidinedones, sulphonylureas, dipeptidyl peptidase-4 (DPP4) inhibitors such as saxagliptin or insulin.[8]

  *SGLT2 inhibitors are not recommended as initial monotherapy. Metformin is still considered first choice in newly diagnosed T2DM patients. SGLT2 inhibitors may be considered as initial starting therapy in patients where metformin is not tolerated or is contraindicated.[2,3]

Pharmacokinetics

Dapagliflozin, empagliflozin and canagliflozin are selective SGLT2 inhibitors and are dosed orally.[2]

Dosing

Dapagliflozin: 10 mg orally once daily for monotherapy and add-on combination therapy.[8]

Canagliflozin: 100 mg starting dose once daily, increasing to 300 mg daily if necessary.**[2](emc)[#]

Empagliflozin: 10 mg starting dose, increasing to 25 mg once daily if necessary.**[2](emc)[#]

**Dose increase only acceptable in patients with eGFR ≥ 60 ml/min/1.73 m^2.

If SGLT2 inhibitors are to be used as add-on combination therapy with insulin or an insulin secretagogue, it may be necessary to reduce the dose of insulin or insulin secretagogue, such as sulphonylureas, in order to decrease the risk of hypoglycaemia.[9]

	Dapagliflozin[9]	Empagliflozin[10]	Canagliflozin[11]
Absorption	Rapidly and well absorbed after oral administration. Bioavailability: 78% Effect of food not considered clinically relevant and therefore may be taken with or without food.	Rapidly absorbed after oral administration. Effect of food not considered clinically relevant and therefore may be taken without regard to food.	Rapidly absorbed after oral administration. Bioavailability approximately 65% Can be taken with or without food, but is recommended to be taken before the first meal of the day.[6]
Distribution	Approximately 91% protein bound	Approximately 86% plasma protein bound	99% plasma protein bound
Metabolism	Extensively metabolised in liver	Minimal metabolism via glucuronidation[2]	Extensively metabolised in liver
Excretion	Half-life (t1/2) is 12.9 hours. 75% excreted in urine 21% excreted in faeces	Half-life (t1/2) is 12.4 hours. 54% excreted in urine 41% excreted in faeces	Half-life (t1/2) is 10.6-13.1 hours depending on dose. 33% excreted in urine 41% excreted in faeces

Efficacy

SGLT2 inhibitors rely on kidney function. In patients with chronic kidney disease (CKD), SGLT2 inhibitors may therefore have a reduced effect.[2]

Large clinical studies of SGLT2 inhibitors in type 2 diabetes have shown these agents to have beneficial effects on glycaemic control, weight and blood pressure.[12]

Glycaemic control

- Clinical trials have shown that for every 1% decrease in haemoglobin that is glycated (HbA_{1c}), there is around a 30% decrease in microvascular complications in patients with T2DM.[5]

In general, dapagliflozin, empagliflozin and canagliflozin have shown an improvement in HbA_{1c} levels with changes averaging 0.5%–1%.[5]

- The percentage of patients with T2DM who achieve their target HbA_{1c} is also an important parameter.

The table below (Table 1) are results of a dapagliflozin monotherapy trial compared to placebo, and a dapagliflozin added to metformin trial compared to placebo.[2]

Weight control

A reduction in body weight of about 1–5 kg is associated with SGLT2-inhibition. Weight loss is primarily due to a decrease in fat mass, while only a small proportion is due to volume depletion. SGLT2 inhibitors when used in combination with insulin may decrease or offset the weight gain due to insulin.[6]

Blood pressure

A decrease in systolic and diastolic blood pressure is seen with SGLT2 inhibitors. Initially, this decrease in blood pressure is mainly due to osmotic diuresis, and subsequently, inhibition of the renin-angiotensin system.[6]

Macrovascular (cardiac) events

The prospective EMPA-REG OUTCOME trial demonstrated a substantial reduction in CV death and hospitalisation for heart failure in patients treated with empagliflozin.[13] The CVD-REAL study, a real-world study, which compared cardiovascular outcomes in new users of SGLT2 inhibitors versus other glucose-lowering drugs, also showed a lower risk of hospitalisation for heart failure and death in patients treated with SGLT2 inhibitors, suggesting a class effect of SGLT2 inhibitors on cardiovascular outcomes.[14] Results from the canagliflozin trial (CANVAS) show similar cardiovascular results to the EMPA-REG trial.[16] Prospective dapagliflozin CV outcomes trial (DECLARE) is therefore also likely to support the findings from the EMPA-REG OUTCOME trial.[15]

Uric acid

Use of SGLT2 inhibitors is associated with a decrease in serum uric acid.[2] This benefit of reduction in uric acid levels is decreased if insulin is prescribed with the SGLT2-inhibitor.[6]

Safety

Renal precautions

As SGLT2 inhibitors depend upon renal function for their activity, renal function will need to be assessed prior to their use.[7]

Dapagliflozin is not recommended for use in patients with moderate to severe renal impairment (creatinine clearance (CrCl) < 60 ml/min or estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2).[9,12] If, during therapy with dapagliflozin, CrCl or eGFR falls below previously mentioned levels, the treatment with dapagliflozin should be discontinued.[9]

Empagliflozin and canagliflozin should not be initiated if CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m^2 and should be discontinued if eGFR persistently falls below 45 ml/min/1.73 m^2 or CrCl is persistently below 45 ml/min.[10,11]

Table 1

	Dapagliflozin monotherapy vs. placebo		Dapagliflozin combination vs. placebo	
	Dapagliflozin 10 mg monotherapy	Placebo group	Dapagliflozin 10 mg in combination with metformin	Placebo group
% of patients achieving HbA_{1c} < 7.0%	50.8–51.6	31.6–34.6	40.6	25.9

Hypotension and hypovolaemia

Osmotic diuresis is associated with SGLT2 use, which may lead to hypovolaemia and orthostatic hypotension.[6] Volume depletion may also lead to a decrease in glomerular filtration rate as a result of a minimal increase in serum creatinine and blood urea.[6]

Hypoglycaemia

Although the risk of hypoglycaemia is low with SGLT2 use, hypoglycaemia may occur when these medicines are combined with other anti-diabetic agents that tend to cause hypoglycaemia (e.g. insulin or the sulphonylureas).[6]

Urogenital tract infections

As a consequence of SGLT2 inhibition, the increased glucose in the urine may encourage bacteria and other micro-organisms to grow, leading to urogenital infections and/or urinary tract infections.[1,2] Women are more likely to develop mycotic genital infections (i.e. vaginal thrush).[3] The increase in glycosuria may also lead to polyuria and nocturia.[2]

Diabetic ketoacidosis

Infrequent reports of ketoacidosis have been associated with SGLT2-inhibitor use. Patients who are susceptible to ketoacidosis, or exhibit symptoms of ketoacidosis, should not have SGLT2-inhibitor therapy initiated, and those taking the SGLT2-inhibitor should discontinue therapy.[12] Ketoacidosis may be triggered by a decreased insulin dose, a decrease in food and fluid consumption, or a significant illness.[2]

Bone mineral density

Bone fracture has been associated with SGLT2 use (canagliflozin). One reason for this may be due to orthostatic hypotension causing dizziness, imbalance and a subsequent fall.[7] Alternatively, since the renal tubule is also the site for calcium/phosphate homeostasis, the use of SGLT2 inhibitors may possibly affect bone metabolism thereby affecting bone density.[2,7]

Interactions

SGLT2 inhibitors may enhance the diuretic effect of thiazide and loop diuretics, leading to dehydration and hypotension.[9,10,11] There is an increased risk of hypoglycaemia when SGLT2 inhibitors are used in combination with insulin or insulin secretagogues (such as sulphonylureas).[9,10,11]

Important prescribing points

- Renal function should be assessed prior to initiation of SGLT2 therapy and intermittently thereafter.[2]
- Patients presenting with symptoms of ketoacidosis (e.g. nausea, vomiting, shortness of breath, or abdominal pain) while taking SGLT2 inhibitors, should be immediately assessed for ketoacidosis and upon confirmation of diagnosis, the SGLT2 agent immediately discontinued.[5,12]
- To reduce the risk of hypoglycaemia, the insulin or insulin secretagogue dose may need to be decreased when used in combination with a SGLT2-inhibitor.[2]
- Factors associated with increased fracture risk should be assessed before initiating SGLT2 therapy.[2]
- Patients who are taking loop diuretics, are volume-depleted, or have other factors that may predispose them to hypotension or fluid loss (e.g. gastrointestinal illness), should have their volume-depletion corrected before initiating SGLT2 therapy.[2]
- Adequate hydration should be emphasised to patients taking SGLT2 inhibitors to reduce the risk of dehydration, hypotension and urinary tract infections.[3]

In summary

- The SGLT2 inhibitors offer a new therapeutic approach to reducing blood glucose levels in patients with type 2 diabetes by working at the level of the kidney.[1,2,3]
- SGLT2 inhibitors, given their insulin-independent mechanism of action, are associated with very low rates of hypoglycaemia in clinical studies.[1]
- Beyond improving glucose control, SGLT2 inhibitors offer potential benefits by reducing body weight and blood pressure.[6,15]
- SGLT2 inhibitors are usually recommended as add-on therapy, e.g. to metformin, or another glucose-lowering agent.[15]

emc = electronic medicines compendium (UK)

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